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Early cardiovascular structural and functional abnormalities as a guide to future morbid events

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Abstract

Aims: Our aim was to evaluate the predictive value of a battery of 10 non-invasive tests of cardiovascular structural and functional health on the future risk of cardiovascular morbid events.

Methods and Results: A total of 1900 asymptomatic adults concerned about their risk for cardiovascular disease underwent non-invasive assessment with 10 tests of vascular and cardiac structure and function. A disease score (DS) was calculated for each individual based on these 10 tests. Follow-up (mean 9.2 years) for cardiovascular morbidity and mortality was available for 1442 individuals (mean age 53.2 years, 48.2% women). Those in the lowest DS tertile (0–2) experienced 0.16 cardiovascular events per 100 patient-years (PY), those in the middle tertile (3–5) experienced 0.86 events per 100 PY, and those in the highest tertile (6+) experienced 1.3 events per 100 PY ($p < .001$). Sensitivity analysis, assuming a neutral effect of DS on projected events in subjects not followed, did not alter statistical significance. Risk assessment using the Framingham risk score (FRS) also predicted morbid events but the two methods differed in identifying individuals at high risk. The net reclassification index was improved by 0.11 ($p = 0.01$) when DS was added to FRS.

Conclusions: Assessing the biological disease process in the arteries and heart of asymptomatic adults provides a guide to the risk of a future cardiovascular morbid event. Larger and longer studies are needed to determine whether risk factor algorithms, the severity of the biological process or some combination is the optimal method for identifying individuals in need of intervention to delay morbid events.

Keywords

Artery structure and function, cardiac structure and function, risk factors, cardiovascular morbid events

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Introduction

Cardiovascular morbid events (CVMEs) usually occur as a complication of abnormal function or structure of the arteries or heart.[1,2] The risk of an individual suffering a future CVME, however, is generally calculated not from severity of these cardiovascular abnormalities but rather from risk factors: demographic and biometric measurements that are statistically associated with the risk of a CVME.[3–5] Although non-invasive techniques now make a comprehensive assessment of the health of the arteries and heart possible, such detection of early vascular and cardiac abnormalities as an independent guide to the risk of future CVMEs has not been thoroughly evaluated.

The Rasmussen Center for Cardiovascular Disease Prevention opened in 2000 to provide asymptomatic individuals with an evaluation of cardiovascular health in an effort to identify those with early

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abnormalities likely to progress and thus potentially to benefit from preventive therapy.[6] The center performs a 1-hour non-radiological assessment (non-invasive except for blood sampling) of the function and structure of representative large arteries, small arteries and the left ventricle, which collectively should serve as a guide to the severity of target organ disease and thus for the likelihood of most CVMEs. The 10 tests employed yield a disease score (DS) which was developed to define the severity of cardiovascular abnormalities, the equivalent of early disease. A preliminary report of the relation between the DS and future CVME supported the hypothesis that this comprehensive assessment of vascular and cardiac health could serve as a guide to future risk, but the analysis was based on only 35 CVMEs over a median follow-up of 3 years.[7]

Longer follow-up of a larger population with substantially more CVMEs now provides the basis for a more robust analysis of: (a) whether the absence of disease based on a low DS can identify individuals who are at very low risk and may not need intervention; (b) whether the magnitude of DS elevation serves as a guide to the likelihood of future CVME; and (c) whether the DS provides similar or different discrimination of risk compared with that of the traditional risk factor assessment using population-based algorithms.[3–5]

Methods

Participants and measurements

Individuals referred or self-referred for evaluation at the Rasmussen Center have no symptoms of disease and no history of a prior CVME. They underwent a standard protocol consisting of a series of tests that assess the functional and structural health of the large conduit arteries, the small pre-capillary arteries, and the left ventricle. These three target organs were selected because they were assumed to represent the cause of most if not all CVMEs, including those involving the heart, the brain, and the peripheral vasculature. The goal was to select tests that could all be carried out non-invasively and without radiation, in one room, in one-hour, by a single technologist. The 10 tests performed are:

1. Resting, sitting blood pressure (BP) measurement
2. Radial pulse contour analysis (RPCA) for calculation of small artery elasticity (C2)[8]
3. RPCA for calculation of large artery elasticity (C1)
4. BP change during 3-minutes of upright treadmill exercise at 5 metabolic equivalents
5. Bilateral retinal photography to assess microvascular structural abnormalities
6. A urine test for laboratory assessment of microalbumin/creatinine ratio
7. Bilateral carotid ultrasound for measurements of wall thickness and detection of atherosclerotic plaques
8. An electrocardiogram to detect cardiac abnormalities
9. Left ventricular ultrasound to assess left ventricular structure and function
10. A blood test for assessment of N-terminal pro-B-type natriuretic peptide.

The 10 tests of function and structure are each graded and scored as normal (score = 0), borderline abnormal (score = 1), or abnormal (score = 2), as previously described.[6,7] The normal range of C1 and C2 and carotid ultrasound measurements are adjusted for age and sex. The sum of the 10 test scores provides a DS which can range from 0 (all tests normal) to 20 (all tests abnormal). Participants also undergo blood tests for measurements of total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, blood sugar and high sensitivity C-reactive protein. Smoking history is also obtained. These measurements are not part of the DS, but some are used in calculating the population-based risk scores. A nurse practitioner also reviews the participant's medical history, performs a physical exam focused on the cardiovascular system and provides lifestyle counseling. All participants and their primary care providers receive a full report of findings and management recommendations from a cardiologist who reviews all the data. Participants sign consent forms agreeing to their data being used for research purposes and their being monitored for vital status and the development of CVME. They are encouraged to return for follow-up testing at intervals from 1 to 5 years but there is no formal follow-up protocol. The study was approved by the University of Minnesota Institutional Review Board.

Follow-up

Follow-up for survival and morbid events was undertaken in 2015 for the 1900 participants enrolled between December 2000 and August 2013. Event ascertainment was conducted through examination of electronic medical records, a Minnesota death registry, a questionnaire sent to those without available medical records, and telephone calls to individuals when needed. All identified CVMEs were adjudicated by DAD or JNC without knowledge of the DS by review of medical records and, when necessary, communication with individual participants. Cause of death was determined by examining medical records or by using the ICD-10 codes provided in the Minnesota

Department of Health records. Data cutoff for CVME was 30 June 2015.

Non-fatal CVME included all documented events that could be attributed to abnormalities of the large or small arteries or the left ventricle. These included myocardial infarction (MI), severe angina requiring reperfusion, stroke, documented transient cerebral ischemic attacks (TIA), heart failure requiring hospitalization and peripheral vascular disease requiring reperfusion.

Statistical methods

Participant characteristics were described using the mean and standard deviation for normally distributed variables and log-transformed for non-normally distributed variables. Median values with interquartile range were used to describe the DS and risk factor algorithm scores. Test for trends were used to compare baseline factors across DS categories. Comparisons between subgroups employed *t*-tests, Wilcoxon rank tests and chi-square tests as appropriate. Risk scores were calculated for each participant using published equations.[3–5]

DS was categorized into 3 levels: 0–2 (''no disease''), 3–5 (''early disease''), and 6 and higher (''advanced disease''). Kaplan–Meier curves for time to CVME were calculated for each category. Time zero was considered the date of the baseline examination. The log-rank test was used to compare DS groups. Participants known not to be deceased and with no reported CV events were censored on 30 June 2015, and those who died from non-cardiovascular causes were censored at date of death. Participants with unknown morbidity status after baseline were excluded. Cox-regression analysis was used to compute hazard ratios (HR) by DS. In three participants with a CVME, the date of the event could not be verified, and their data are excluded in time-to-event analysis.

Sensitivity analysis was performed to address unknown event status due to non-contact of 24% of participants. In this analysis, we estimated the number of missing events based on the observed rate of events, the amount of missing follow-up time, and the ratio of the Framingham Risk Score (FRS) of participants contacted vs the FRS of participants not contacted. FRS was utilized as the primary risk comparator because it utilizes similar morbid event assessments—complications of large artery, small artery and left ventricular abnormalities—as does the DS assessment. We apportioned the estimated 32 missing events evenly across the DS categories, taking into account the amount of follow-up time missing in each DS category.

To assess whether the DS added significant predictive ability above the FRS, we employed reclassification methods as described by Pencina.[9] We estimated for each participant their 10-year risk of a CVME using two Cox-regression models: (a) including the FRS only; and (b) including the FRS and the DS. We then divided the estimated probability (based on (a)) into tertiles of estimated risk and cross-classified participants (3×3 table) using the estimates from the two models. From this cross-classification the net reclassification improvement (NRI) was calculated separately for those with and without CVME. Analyses were performed using SAS, version 9.4.

Results

Follow-up cardiovascular disease (CVD) event status through 30 June 2015 was obtained for 1442 (76%) of the 1900 participants. Participants with follow-up exhibited higher levels of calculated baseline risk than those whose follow-up could not be assessed, including an older age (53 ± 11 vs. 48 ± 11years, $p < 0.001$), a higher Framingham 10-year risk (10.8 ± 9.7 vs. 8.6 ± 8.2, $p < 0.001$) and a higher DS (4.6 ± 3.4 vs. 4.1 ± 3.3, $p = 0.003$) (online Supplementary Table 1). Characteristics of participants followed are shown in Table 1.

Table 2 displays baseline characteristics by the three categories of DS. Blood pressure, part of the DS, was the strongest risk factor related to DS. Sex and cholesterol levels were not related to the DS.

During a median follow-up of 9.1 years after initial evaluation, 102 of the 1442 participants experienced a CVME (0.80 events per 100 person years (PY). Of the 102 first CVME, 6 were deaths, 19 were MIs, 22 were strokes or TIAs, 13 were heart failure, 39 were angina, and 3 were peripheral vascular disease. Few participants had multiple CVD events: two participants had two events (MI and CVD death, angina and peripheral vascular disease (PVD)) and one participant had four CVME (angina, heart failure, TIA, and PVD). Risk factor comparisons between those with a CVD event and those without are displayed in Table 3. Age, male sex, body mass index, systolic BP, and glucose were higher in the event group than in the non-event group. In addition, the baseline risk scores and DS were significantly higher in the group who developed an event.

During follow-up, the CVME rate was significantly different among the three baseline DS subgroups (log-rank chi-square (2 df) = 33.72, $p < 0.001$, Figure 1). Six CVME (0.16 events per 100 PY) occurred in the DS 0–2 subgroup, most occurring more than 6 years after initial evaluation. The DS 3–5 subgroup experienced 36 CVME (0.86 events per 100 PY) and the DS 6+ subgroup experienced the highest CVD event rate, 60 events (1.3 events per 100 PY).

Table 1. Baseline characteristics of cohort with follow-up data.

Characteristic	Men	Women	Total
Age (years)	53.0 ± 11.5	53.4 ± 10.9	53.2 ± 11.2
Women (%)	N/A	N/A	695 (48.2)
Smoking (%)	64 (8.7)	28 (4.1)	92 (6.5)
Body Mass Index (kg/m^2)	27.9 ± 4.2	27.4 ± 6.0	27.6 ± 5.1
Systolic BP (mm Hg)	127.2 ± 15.7	123.0 ± 18.6	125.2 ± 17.3
Diastolic BP (mm Hg)	79.9 ± 10.3	75.0 ± 9.8	77.6 ± 10.4
Total Cholesterol (mg/dl)	198.0 ± 38.2	213.0 ± 42.8	205.2 ± 41.2
LDL Cholesterol (mg/dl)	125.3 ± 34.5	129.4 ± 38.6	127.3 ± 36.6
HDL Cholesterol (mg/dl)	44.9 ± 12.0	59.3 ± 18.1	51.9 ± 16.9
Triglycerides (mg/dl)	118 (83–170)	100 (75–142)	110 (78–155)
Glucose (mg/dl)	96.1 ± 15.5	92.3 ± 16.3	94.3 ± 16.0
C-reactive protein (mg/dl)	0.13 (0.07–0.28)	0.18 (0.07–0.43)	0.15 (0.07–0.34)
Antihypertensive drugs (%)	208 (27.8)	168 (24.2)	376 (26.1)
Statin drugs (%)	176 (23.6)	118 (17.0)	294 (20.4)
Framingham 10-year CVD risk	11.8 (6.4–19.0)	5.2 (2.8–8.5)	7.8 (4.1–14.3)
Pooled cohort 10-year CVD risk	5.9 (2.5–12.2)	2.1 (0.9–4.5)	3.4 (1.4–8.2)
European 10-year CVD death risk	2.4 (0.9–5.1)	0.8 (0.2–1.8)	1.4 (0.5–3.4)
Disease score	4.0 (2.0–7.0)	4.0 (2.0–7.0)	4.0 (2.0–7.0)
No. of participants	**747**	**695**	**1442**

Values in cells are mean ± SD, *n* (%), or median (interquartile range).
BP: blood pressure; CVD: cardiovascular disease; HDL: high density lipoprotein; LDL: low density lipoprotein.

Table 2. Baseline characteristics by disease score.

Characteristic	Disease score 0–2	Disease score 3–5	Disease score 6+	*p*-value
Age (years)	47.9 ± 10.1	52.7 ± 10.0	58.4 ± 10.8	<0.001
Women (%)	227 (50.3)	228 (46.6)	240 (47.8)	0.45
Smoking (%)	23 (5.2)	33 (6.9)	36 (7.3)	0.20
Body Mass Index (kg/m^2)	27.2 ± 4.6	27.7 ± 5.4	28.0 ± 5.4	0.01
Systolic BP (mm Hg)	114.1 ± 11.2	122.1 ± 13.9	138.1 ± 16.5	<0.001
Diastolic BP (mm Hg)	73.4 ± 8.3	77.0 ± 9.6	81.9 ± 11.0	<0.001
Total Cholesterol (mg/dl)	201.8 ± 38.5	207.6 ± 42.1	206.0 ± 42.5	0.13
LDL Cholesterol (mg/dl)	125.7 ± 34.1	129.7 ± 38.4	126.3 ± 36.9	0.83
HDL Cholesterol (mg/dl)	51.3 ± 15.6	52.4 ± 17.5	51.9 ± 17.3	0.64
Triglycerides (mg/dl)	107 (77–147)	105 (78–157)	115 (81–167)	<0.003
Glucose (mg/dl)	92.0 ± 13.2	93.7 ± 15.8	96.9 ± 18.0	<0.001
C-reactive protein (mg/dl)	0.12 (0.06–0.29)	0.15 (0.07–0.36)	0.17 (0.07–0.39)	<0.001
Antihypertensive drugs (%)	54 (12.0)	113 (23.1)	209 (41.6)	<0.001
Statin drugs (%)	69 (15.3)	110 (22.5)	115 (22.9)	0.004
Framingham 10-year CVD risk	4.6 (2.4–7.4)	7.6 (4.2–12.4)	13.2 (7.8–22.7)	<0.001
Pooled cohort 10-year CVD risk	1.7 (0.7–3.6)	3.3 (1.5–6.9)	7.1 (3.3–15.8)	<0.001
European 10-year CVD death risk	0.6 (0.2–1.4)	1.3 (0.5–2.9)	3.0 (1.3–7.2)	<0.001
Disease score	1.0 (0.0–2.0)	4.0 (3.0–5.0)	8.0 (7.0–10.0)	N/A
No. of participants	**451**	**489**	**502**	

Values in cells are mean ± SD, *n* (%), or median (interquartile range).
BP: blood pressure; CVD: cardiovascular disease; HDL: high density lipoprotein; LDL: low density lipoprotein.

Table 3. Baseline characteristics by follow-up cardiovascular morbid event status.

Characteristic	Events	No event	*p*-value
Age (year)	61.5 ± 9.7	52.5 ± 11.0	<0.001
Women (%)	33 (32.4)	662 (49.4)	<0.001
Smoking (%)	6 (6.2)	86 (6.5)	0.90
Body Mass Index (kg/m^2)	28.7 ± 5.5	27.6 ± 5.1	0.04
Systolic BP (mm Hg)	133.0 ± 19.4	124.6 ± 17.0	<0.001
Diastolic BP (mm Hg)	78.0 ± 10.9	77.5 ± 10.3	0.65
Total Cholesterol (mg/dl)	205.2 ± 40.7	205.2 ± 41.3	0.99
LDL Cholesterol (mg/dl)	130.3 ± 33.8	127.1 ± 36.8	0.40
HDL Cholesterol (mg/dl)	48.3 ± 14.4	52.1 ± 17.0	0.03
Triglycerides (mg/dl)	113 (79–154)	110 (78–155)	0.76
Glucose (mg/dl)	99.4 ± 20.2	93.9 ± 15.5	<0.001
C-reactive protein (mg/dl)	0.16 (0.08–0.36)	0.15 (0.07–0.34)	0.22
Antihypertensive drugs (%)	43 (42.2)	333 (24.9)	<0.001
Statin drugs (%)	19 (18.6)	275 (20.5)	0.65
Framingham 10-year CVD risk (%)	18.3 (10.6–27.5)	7.4 (3.9–13.2)	<0.001
Pooled cohort 10-year CVD risk (%)	12.3 (5.3–17.4)	3.2 (1.3–7.3)	<0.001
European 10-year CVD death risk	1.3 (0.4–3.1)	4.3 (2.1–8.4)	<0.001
Disease score	6.0 (4.0–8.0)	4.0 (2.0–6.0)	<0.001
No. of participants	**102**	**1340**	

Values in cells are mean ± SD, *n* (%), or median (interquartile range).
BP: blood pressure; CVD: cardiovascular disease; HDL: high density lipoprotein; LDL: low density lipoprotein.

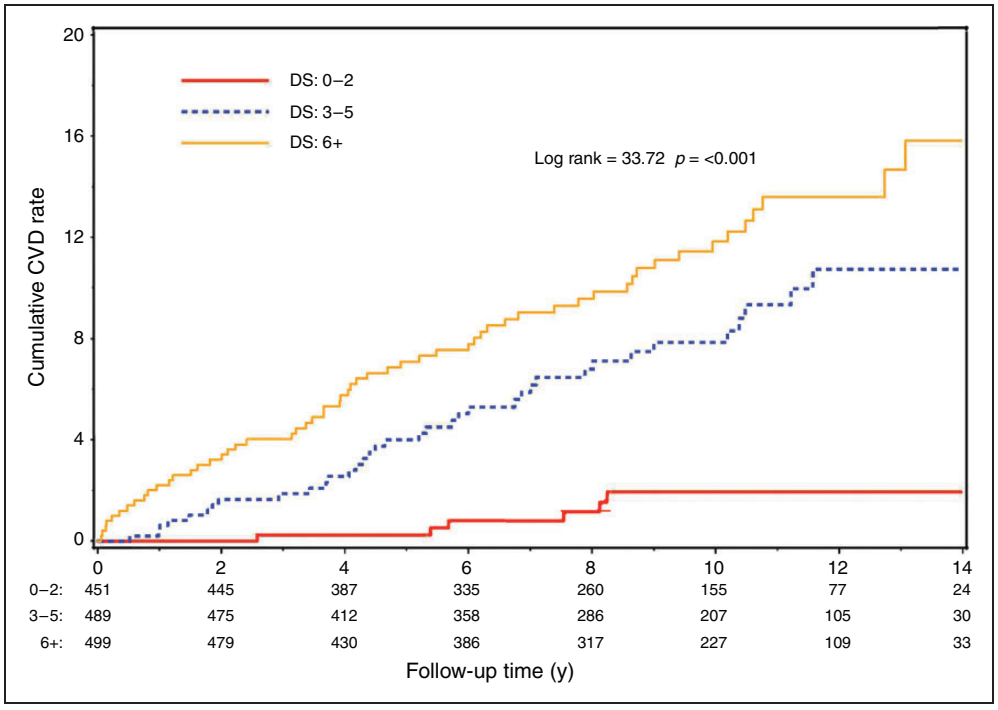

Figure 1. Kaplan–Meier curves depicting the cardiovascular (CV) morbid event rate in the three disease score (DS) subgroups. CVD: cardiovascular disease; y: years.

Table 4. Distribution of Framingham risk scores and disease scores of participants ($n = 1442$).

	Disease score			
Framingham 10-year Risk	0–2 *n* (%)	3–5 *n* (%)	6+ *n* (%)	Total *n* (%)
<5.2	256 (17.75)	164 (11.37)	62 (4.30)	482 (33.43)
5.2–11.6	137 (9.50)	185 (12.83)	154 (10.68)	476 (33.01)
>11.6	58 (4.02)	140 (9.71)	286 (19.83)	484 (33.56)
Total	451 (31.28)	489 (33.91)	502 (34.81)	1442 (100.00)

Table 5. Distribution of 102 cardiovascular morbid events according to Framingham risk score and disease score.

	Disease score			
Framingham 10-year Risk	0–2 *n* (%)	3–5 *n* (%)	6+ *n* (%)	Total *n* (%)
<5.2	2 (1.96)	6 (5.88)	1 (0.98)	9 (8.82)
5.2–11.6	2 (1.96)	9 (8.82)	11 (10.78)	22 (21.57)
>11.6	2 (1.96)	21 (20.59)	48 (47.06)	71 (69.61)
Total	6 (5.88)	36 (35.29)	60 (58.82)	102 (100.00)

HR were 5.4 (95% confidence interval (CI): 2.3–12.9) and 8.3 (95% CI 3.6–19.2) in the DS 3–5 and DS 6+ subgroups, respectively, compared with the DS 0–2 group. In addition, the DS was significantly related to CVME when entered into the Cox model as a continuous variable.

To determine which components of the DS were associated with CVME we included each component score in separate Cox regression models. The results are displayed in online Supplementary Table 3. Each component was significantly related to CVME except large artery elasticity and microalbuminuria. The electrocardiogram and the brain natriuretic peptide (BNP) score had the strongest associations with CVME (HR = 1.9 each). Adjusting each component for age and sex diminished the associations with CVME but the overall DS was still significant (online Supplementary Table 4). BP is a powerful marker for risk because it serves as both a factor contributing to CVME and a manifestation of vascular disease itself.[10] When adjusted for systolic blood pressure, some of the individual components of the DS were no longer significantly related to CVME but the overall DS remained significantly predictive (online Supplementary Table 4). Cox regression analysis using C1, C2, BNP, and albumin as continuous variables showed both C1 and C2 to be significantly inversely related to CVME, BNP to be significantly positively related with CVME, and urine albumin not associated with CVME.

Discordance between the DS and FRS was explored by examining tertiles of both measurements. In more than half the individuals the DS and FRS placed the individuals into different tertiles of risk, both in the entire population ($n = 1442$) (Table 4) and in the subset who experienced a CVME ($n = 102$) (Table 5).

A summary of the reclassification analysis is given in Table 6. Among the 102 participants with a CVME, 11 participants were reclassified as higher risk (green shading) when the DS was added to the FRS in the Cox model compared with 7 participants who were reclassified as lower risk (orange shading). The NRI for participants with CVME was 0.049. Among the 1340 participants without a CVD event, 255 participants were reclassified as lower risk (green shading) when the DS was added to the model, compared with 157 participants who were reclassified as higher risk (orange shading) (NRI = 0.073). The NRI when including participants with and without a CVD event was 0.122 ($p = 0.01$).

In order to correct for incomplete follow-up, we explored how much the CVD risk across DS categories could change if the 24% missing participants had been followed. Based on the FRS of participants that were not successfully contacted we estimated that 32 CVME were missing. If we apply equal rates of missing events across the three DS categories (i.e. no association between DS and CVME) the rate ratio of DS 3–5 compared with DS 0–2 decreases from 5.4 to 2.5

Table 6. Reclassification among participants who experienced a cardiovascular morbid event and those who did not experience a cardiovascular morbid event during follow-up.

	Model with Framingham risk score and disease score			
	<4.8 %	4.8–6.6%	>6.6%	Total
Participants with CV morbid event				
Model with FRS only				
<4.8 %	8	1	0	9
4.8–6.6%	4	8	10	22
>6.6%	0	3	68	71
Total	12	12	78	102
Participants without CV morbid event				
Model with FRS only				
<4.8 %	401	63	5	469
4.8–6.6%	168	201	89	458
>6.6%	8	79	326	413
Total	577	343	420	1340

NRI = 11/102–7/102 = 0.049 for CVD events.
NRI = 255/1340–157/1340 = 0.073 for non-CVD events.
NRI = 0.112 total, $z = 2.56$, $p = 0.01$.
CV: cardiovascular; CVD: cardiovascular disease; FRS: Framingham risk score; NRI: net reclassification improvement.
In "Participants with CV morbid event" table, orange shading is high risk, while green is low risk. In "Participants without CV morbid event" table, orange shading is high risk, while green is low risk.

(online Supplementary Table 3) and the rate ratio between DS 6+ and DS 0–2 decreases from 8.3 to 3.6, but statistical significance of the difference between the groups was retained.

Discussion

This follow-up of up to 15 years in individuals with no prior history of CVD has confirmed the earlier preliminary analysis[7] suggesting that the severity of functional and structural vascular and cardiac abnormalities is predictive of future CVMEs. By using a 10-test DS, calculated by classifying each of the tests as normal, borderline, or abnormal, one-third of the population had essentially normal scores and a very low CVME rate (<2% at 10 years of follow-up). The other two-thirds of the population with a DS of more than two could be divided into two nearly equal groups with early (DS 3–5) and advanced (DS 6+) abnormalities of function and structure. The CVME rate in the early disease group was 7.5% and in the advanced disease group 11.9% at 10 years of follow-up ($p < 0.001$ vs no disease, $p < 0.05$ comparing early and advanced disease).

Among the 1900 patients evaluated in our Center during the study interval, 458 (24%) had no electronic medical record visits to document their health on 30 June 2015 and could not be reached by mail or by phone. When the estimated number of events in this subpopulation were equally distributed across the DS subgroups, the subgroup event rate difference remained statistically significant.

Target organ assessment

These data represent the first documentation that in asymptomatic adults the absence of non-invasively assessed functional and structural cardiovascular abnormalities identifies individuals at a very low risk for future morbid events. Furthermore, the data confirm that the severity of these abnormalities predict the future likelihood of CVMEs. These findings thus suggest that the non-invasive testing we have utilized provides a window into the progressive biological process that leads to CVMEs (Figure 2).

The 10 tests utilized to calculate the DS were selected because of their collective ability to assess functional and structural abnormalities of the large conduit arteries, the small microcirculatory arteries, and the left ventricle, and because they could all be performed in a single room in less than an hour. All the tests contributed significantly to the DS and 8 of the 10 were independently predictive of CVME. Whether any could be eliminated without loss of predictive value needs further study.

Risk assessment

The goal of risk assessment is to identify individuals likely to benefit from lifestyle or pharmacologic

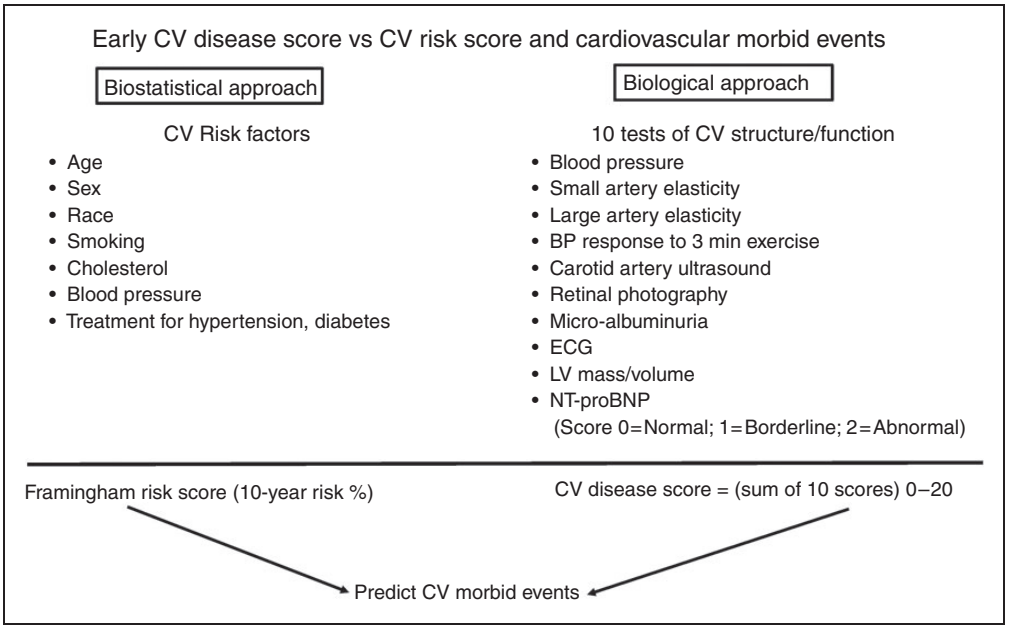

Figure 2. Contrast between the current biostatistical approach to identifying risk and the proposed biological approach.
BP: blood pressure; CV: cardiovascular ECG: electrocardiogram; LV: left ventricle; NT-proBNP: N-terminal pro-B-type natriuretic peptide.

intervention. That should include all adults who would otherwise sustain a CVME during their lifetime. For that purpose, a 10-year morbid event rate is inadequate for separating high and low-risk individuals. The improved risk assessment we identified when DS was added to FRS is based on an average of only 9 years of monitoring. Longer follow-up in larger populations is needed to more effectively separate those who will and will not have their lives interrupted by a CVME.

The use of tertiles of the population to categorize risk is appropriate, since about one-third of the American population dies from cardiovascular morbid events.[10] It is likely that considerably more individuals harbor advanced CVD but have their lives terminated by competing morbid events. Intervention on more than the highest tertile is therefore probably necessary to effectively prevent or delay cardiovascular mortality.

The identification of a substantial low-risk group, whose CVME rate was so low that therapy need not be considered, could relieve the burdens of anxiety and intervention in a sizeable population. The ease of performance of the 10-test evaluation also provides the opportunity to track progression of functional or structural abnormalities that may eventually require intervention.

Although detection of cardiovascular structural and functional abnormalities offers the potential of a more individualized approach to risk identification, a more extensive comparison with the use of risk factor algorithms is required. In the present study FRS and DS were often discordant in recognizing individuals in need of treatment. A much longer follow-up in larger populations is necessary to determine if assessment of the biologic process in the cardiovascular system offers an improvement in identifying individuals in need of lifestyle or drug therapy to prevent or delay morbid events.

Limitations

The population included in this study is self-selected, concerned about their health and from a single center. Only 75% of them could be tracked for morbid events. Replication of these findings in a more diverse, randomly selected population is required for confirmation.

Author contribution

DAD provided oversight to the data collection, data analysis and outcome assessment; SD and GG performed biostatistical support and data analysis and interpretation; LH and NF collected and analyzed all patient data; CC and JL collected all follow-up and outcome data; JNC created the testing protocol, developed support for the study, contributed to oversight of the data collection and wrote the manuscript.

Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Jay N Cohn has an equity position in Cardiology Prevention, LLC, which has licensed patents on methods to detect early cardiovascular disease.

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Supplemental material

Supplemental material for this article is available online.

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